(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 April 2002 (04.04.2002)

PCT

(10) International Publication Number
WO 02/26731 A2

(51) International Patent Classification[7]: C07D 401/00

(21) International Application Number: PCT/US01/30314

(22) International Filing Date: 1 October 2001 (01.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/236,385 29 September 2000 (29.09.2000) US

(71) Applicant *(for all designated States except US)*: **COR THERAPEUTICS, INC.** [US/US]; 256 East Grand Avenue, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHU, Bing-Yan** [CA/US]; 135 Lois Lane, Palo Alto, CA 94303 (US). **HUANG, Wenrong** [CN/US]; 7723 Huntridge Lane, Cupertino, CA 95014 (US). **ZHANG, Penglie** [CN/US]; 251 Winchester Court, Foster City, CA 94404 (US). **JIA, Zhaozhong, Jon** [CN/US]; 1576-E Marina Court, San Mateo, CA 94404 (US). **BAO, Liang** [CN/US]; 386 Goodwin Drive, San Bruno, CA 94060 (US). **WU, Yanhong** [CN/US]; 731 Catamaran Street #2, Foster City, CA 94404 (US). **SCARBOROUGH, Robert, M.** [US/US]; 22 Greenbrier Court, Half Moon Bay, CA 94019 (US).

(74) Agents: **LEE, Christine, S.** et al.; Morgan, Lewis & Bockius LLP, 1800 M. Street, NW, Washington, DC 20036 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/26731 A2

(54) Title: QUATERNARY AMIDINO BASED INHIBITORS OF FACTOR XA

(57) Abstract: Novel quaternary amidino-containing compounds of the general formulae (I), (II), (III), (IV), (V) and (VI): including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa are described. Compositions containing such compounds are also described. The compounds and the compositions are useful *in vitro* or *in vivo* for preventing or treating conditions in mammals characterized by undesired thrombosis.

QUATERNARY AMIDINO BASED INHIBITORS OF FACTOR Xa

Field of the Invention

The invention relates to novel quaternary amidino-containing compounds including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel quaternary amidino-containing compounds including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives factor Xa-inhibiting compounds, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by undesired thrombosis or coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the

focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

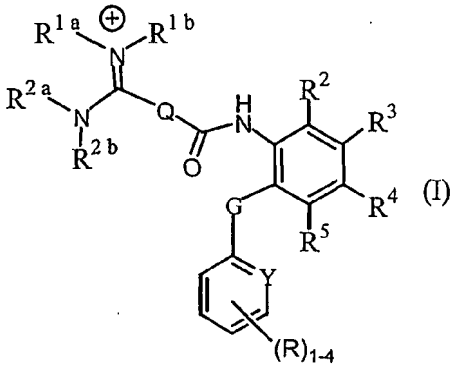
There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which

selectively inhibit factor Xa or its precursors. Compounds are needed which selectively or preferentially bind to Factor Xa. Compounds with a higher affinity for binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability or other pharmacologically desirable properties.

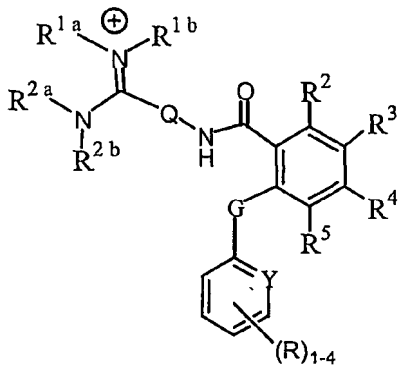
Summary of the Invention

The present invention relates to novel piperazine-containing compounds including their pharmaceutically acceptable isomers, salts, hydrates, solvate and prodrug derivatives, which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. According to the invention, the compounds can act as potent and highly selective inhibitors of isolated Factor Xa or when assembled in the prothrombinase complex. The invention also provides compositions containing such compounds. The compounds of the invention may be used as diagnostic reagents or as therapeutic reagents for disease states in mammals which have coagulation disorders. Thus, the invention further provides methods for preventing or treating a condition in a mammal characterized by undesired thrombosis by administration of a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. Optionally, the methods of the invention comprise administering a pharmaceutical composition of the invention in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant. According to the invention, such conditions include, for example, any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples (e.g. stored blood products and samples).

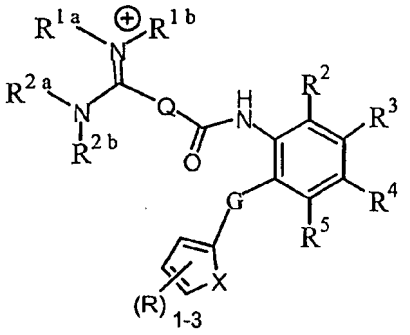
The invention provides a compound of the general formulae (I), (II), (III), (IV), (V), or (VI):



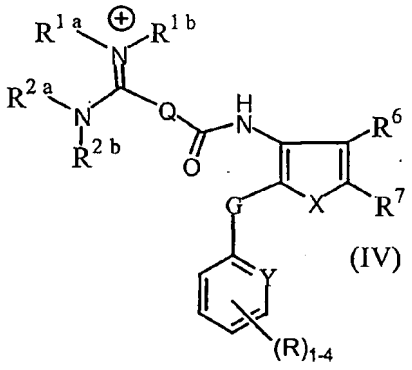
(I)



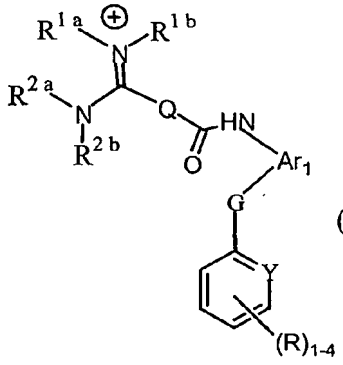
(II)



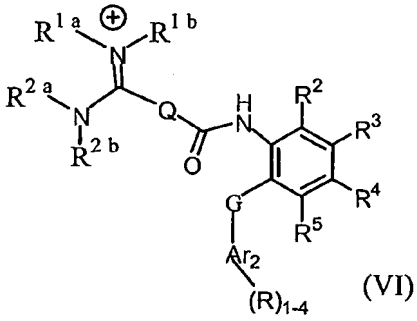
(III)



(IV)



(V)



(VI)

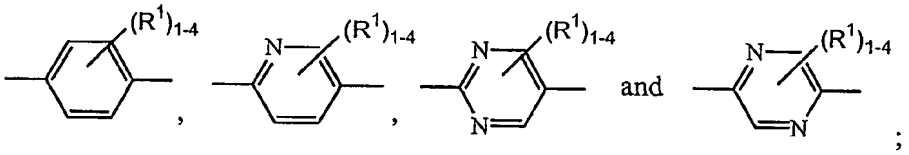
wherein:

R^{1a} and R^{1b} are each independently a member selected from the group consisting of: C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{1a} and R^{1b} or R^{1a} and R^{2a}, as set forth below, taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or

heteroaromatic quaternary amidino group, which optionally contains heteroatoms of N, O or S; R^{1a} or R^{1b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

R^{2a} and R^{2b} are each independently a member selected from the group consisting of: C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{2a} and R^{2b} or R^{2a} and R^{1a}, as set forth above, taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or heteroaromatic amino group, which optionally contains heteroatoms of N, O or S; R^{2a} or R^{2b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

Q is a member selected from the group consisting of:



;

R^1 is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, haloC_{1-6}alkyl, -OH, -OC_{1-6}alkyl, -OhaloC_{1-6}alkyl, $-NO_2$, -CN, -OC_{1-6}alkylCOOH, -OC_{1-6}alkylCOOC_{1-6}alkyl, -OC_{1-6}alkylCONR$_a$R$_b$, -NR$_a$C$_{1-6}$alkylCOOH, -NR$_a$C$_{1-6}$alkylCOOC_{1-6}alkyl, -NR$_a$C$_{1-6}$alkylCONR$_a$R$_b$, -NR$_a$R$_b$, -NHSO_2C$_{1-6}$alkyl, -NHCOC_{1-6}alkyl, -NHCOC_{1-6}alkylNR$_a$R$_b$, –SC_{1-6}alkyl, -SO_2C$_{1-6}$alkyl, SOC_{1-6}alkyl, or –SO_2NR$_a$R$_b$;

R_a and R_b are independently H, -C_{1-6}alkyl, haloC_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl C_{3-8}cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R_a and R_b taken together with the nitrogen to which they are attached forms a heterocyclic or heteroaromatic amine group and which optionally contains heteroatoms of N, O or S and which is

optionally substituted with –BOC, alkyl, acyl, -SO_2C_{1-6}alkyl, -CO_2C_{1-6}alkyl, -COOH, or –$CONR_aR_b$;

R^2, R^3, R^4, and R^5 are independently H, -Cl, -Br, -I, -F, C_{1-6}alkyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, -OH, -Ohaloalkyl, -NO_2, -NHAc, -$NHSO_2Me$, C_{1-6}alkylguanidino, C_{1-6}alkylamidino, -NR_aR_b, -OC_{1-6}alkylOH, -OC_{1-6}alkylOC_{1-6}alkyl, -OC_{1-6}alkylNR_aR_b, -NR_aC_{1-6}alkylOH, -NR_aC_{1-6}alkylOC_{1-6}alkyl, -NR_aC_{1-6}alkylNR_aR_b, -OC_{1-6}alkylCOOH, -OC_{1-6}alkyl$COOC_{1-6}$alkyl, -OC_{1-6}alkyl$CONR_aR_b$, -NR_aC_{1-6}alkylCOOH, -NR_aC_{1-6}alkyl$COOC_{1-6}$alkyl, -NR_aC_{1-6}alkyl$CONR_aR_b$, aryl, heteroary, -SC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, or -$SO_2NR_aR_b$, where R_a and R_b are each as set forth above;

Ar_1 is a six-membered aromatic heterocyclic ring containing 1-3 N atoms; The ring atoms are independently substituted by R^2, R^3, or R^4;

X is -O- or -S-;

G is –C(=O)NH- or –NHC(=O)-;

Y is CH or N;

R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -OC_{1-6}alkyl; and

Ar_2 is a five or six-membered aromatic ring containing 1-3 hetero atoms selected from N, O, and S; The ring atoms are independently substituted by 1-4 R group;

R is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, -OC_{1-6}alkyl, -OH, or -NR_aR_b, where R_a and R_b are each as set forth above;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkynyl" (or "alkinyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkynyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not

limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, naphthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzylhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a

stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocyclic and bicyclic heterocyclic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl,

imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocyclic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

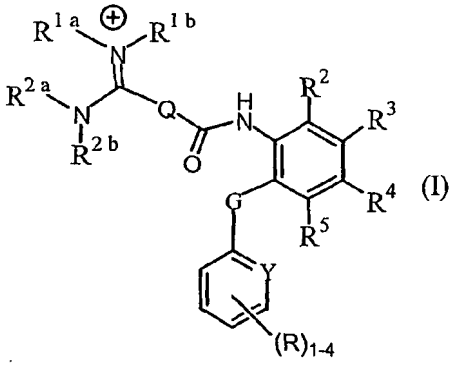
"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any

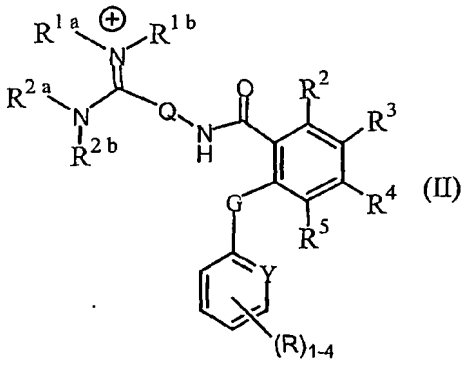
carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

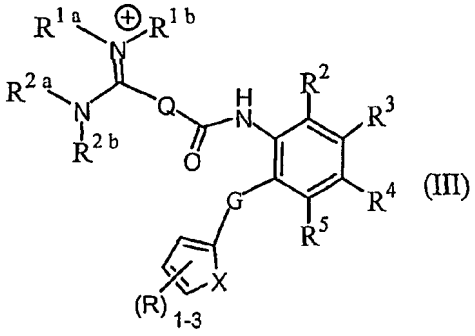
In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Compounds

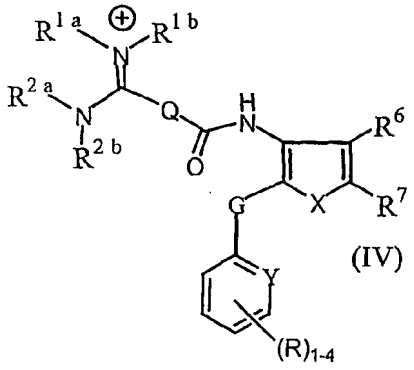
The invention provides a compound of the general formulae (I), (II), (III), (IV), (V), or (VI):


(I)

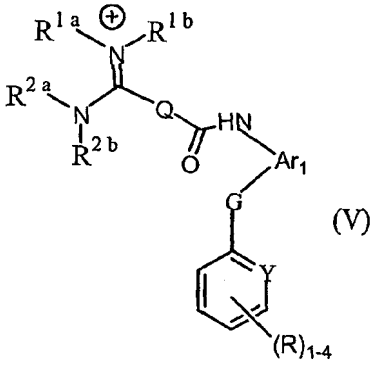

(II)



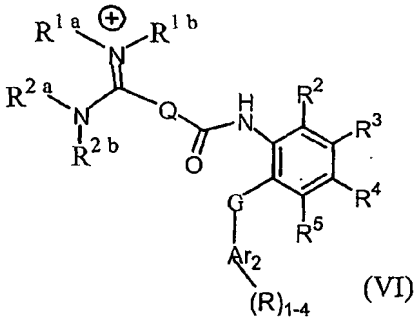
(III)



(IV)



(V)



(VI)

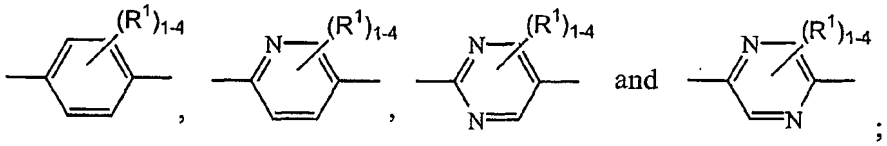
wherein:

R^{1a} and R^{1b} are each independently a member selected from the group consisting of: C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{1a} and R^{1b} or R^{1a} and R^{2a}, as set forth below, taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or heteroaromatic quaternary amidino group, which optionally contains heteroatoms of N, O or S; R^{1a} or R^{1b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

R^{2a} and R^{2b} are each independently a member selected from the group consisting of: C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{2a} and R^{2b} or R^{2a} and R^{1a}, as set forth above, taken together with the nitrogen atom to which they

are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or heteroaromatic amino group, which optionally contains heteroatoms of N, O or S; R^{2a} or R^{2b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

Q is a member selected from the group consisting of:



;

R^1 is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, haloC_{1-6}alkyl, -OH, -OC_{1-6}alkyl, -OhaloC_{1-6}alkyl, -NO_2, -CN, -OC_{1-6}alkylCOOH, -OC_{1-6}alkylCOOC_{1-6}alkyl, -OC_{1-6}alkylCONR$_a$R$_b$, -NR$_a$C$_{1-6}$alkylCOOH, -NR$_a$C$_{1-6}$alkylCOOC_{1-6}alkyl, -NR$_a$C$_{1-6}$alkylCONR$_a$R$_b$, -NR$_a$R$_b$, -NHSO_2C$_{1-6}$alkyl, -NHCOC_{1-6}alkyl, -NHCOC_{1-6}alkylNR$_a$R$_b$, –SC_{1-6}alkyl, -SO_2C$_{1-6}$alkyl, SOC_{1-6}alkyl, or –SO_2NR$_a$R$_b$;

R$_a$ and R$_b$ are independently H, -C_{1-6}alkyl, haloC_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl C_{3-8}cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R$_a$ and R$_b$ taken together with the nitrogen to which they are attached forms a heterocyclic or heteroaromatic amine group and which optionally contains heteroatoms of N, O or S and which is optionally substituted with –BOC, alkyl, acyl, -SO_2C$_{1-6}$alkyl, -CO_2C$_{1-6}$alkyl, -COOH, or –CONR$_a$R$_b$;

R^2, R^3, R^4, and R^5 are independently H, -Cl, -Br, -I, -F, C_{1-6}alkyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, -OH, -Ohaloalkyl, -NO_2, -NHAc, -NHSO_2Me, C_{1-6}alkylguanidino, C_{1-6}alkylamidino, -NR$_a$R$_b$, -OC_{1-6}alkylOH, -OC_{1-6}alkylOC_{1-6}alkyl, -OC_{1-6}alkylNR$_a$R$_b$, -NR$_a$C$_{1-6}$alkylOH, -NR$_a$C$_{1-6}$alkylOC_{1-6}alkyl, -NR$_a$C$_{1-6}$alkylNR$_a$R$_b$, -OC_{1-6}alkylCOOH, -OC_{1-6}alkylCOOC_{1-6}alkyl, -OC_{1-6}alkylCONR$_a$R$_b$, -NR$_a$C$_{1-6}$alkylCOOH, -NR$_a$C$_{1-6}$alkylCOOC_{1-6}alkyl, -NR$_a$C$_{1-6}$alkylCONR$_a$R$_b$, aryl, heteroary,

-SC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, or -$SO_2NR_aR_b$, where R_a and R_b are each as set forth above;

Ar_1 is a six-membered aromatic heterocyclic ring containing 1-3 N atoms; The ring atoms are independently substituted by R^2, R^3, or R^4;

X is -O- or -S-;

G is –C(=O)NH- or –NHC(=O)-;

Y is CH or N;

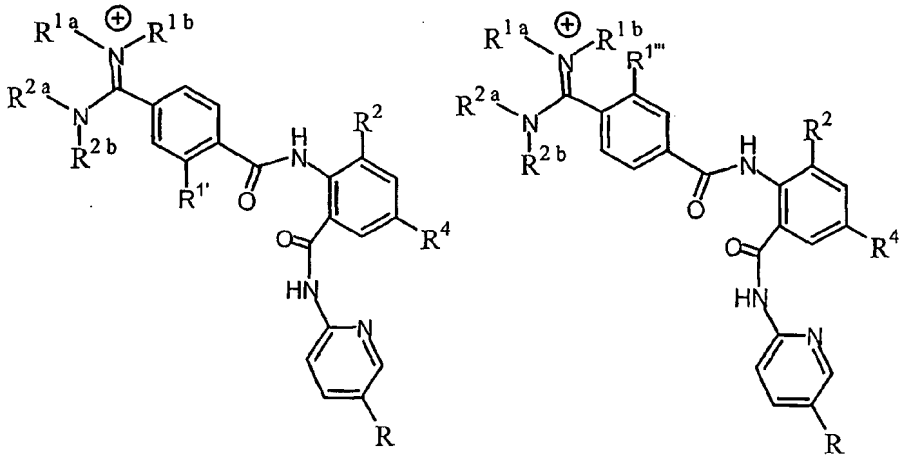
R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -OC_{1-6}alkyl; and

Ar_2 is a five or six-membered aromatic ring containing 1-3 hetero atoms selected from N, O, and S; The ring atoms are independently substituted by 1-4 R group;

R is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, -OC_{1-6}alkyl, -OH, or -NR_aR_b, where R_a and R_b are each as set forth above;

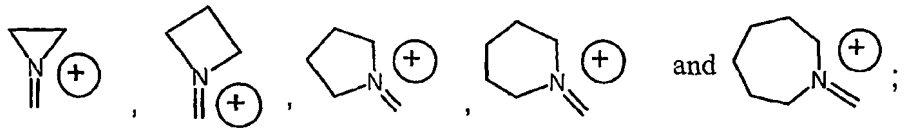
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formula (I-VI) having the following structure:

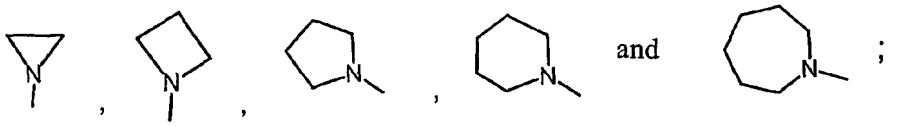


wherein:

R^{1a} and R^{1b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a quaternary ammonium group selected from the group consisting of:



R^{2a} and R^{2b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{2a} and R^{2b} taken together with the nitrogen atom to which they are attached form a heterocyclic amine group selected from the group consisting of:



$R^{1'}$ and $R^{1'''}$ are independently a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, SMe, SO_2Me, or SO_2NH_2;

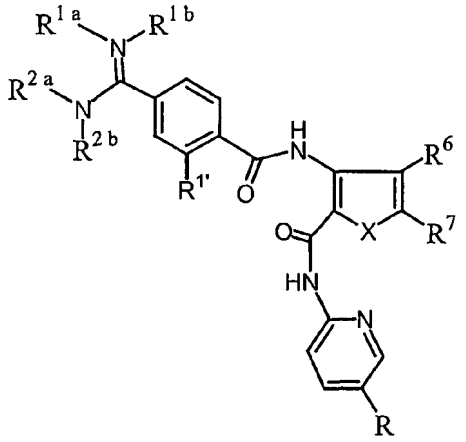
R^2 is a H, -Cl, -Br, -I, -F or $-O-C_{1-6}$alkyl; and

R^4 is a H, -Cl, -Br, -I, -F, $-O-C_{1-6}$alkyl, $-NH-C_{1-6}$acyl, $-NO_2$, $-NHSO_2-C_{1-4}$alkyl, -CN or $-O-(CH_2)_{1-4}-COOH$; and

R is a -Cl, -Br, -I or –F.

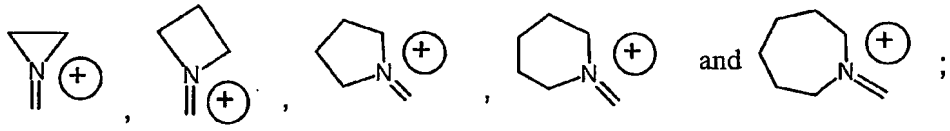
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formula (I-VI) having the following structure:

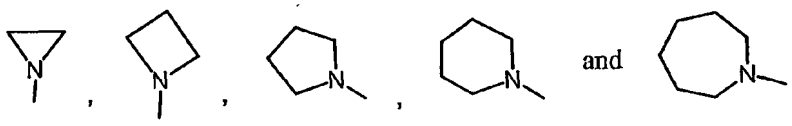


wherein:

R^{1a} and R^{1b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a quaternary ammonium group selected from the group consisting of:



R^{2a} and R^{2b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{2a} and R^{2b} taken together with the nitrogen atom to which they are attached form a heterocyclic amine group selected from the group consisting of:



$R^{1'}$ is a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, SMe, SO_2Me, or SO_2NH_2;

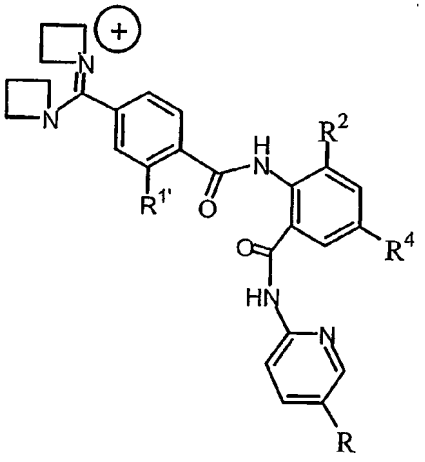
X is -O- or -S-;

R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -OC_{1-6}alkyl; and

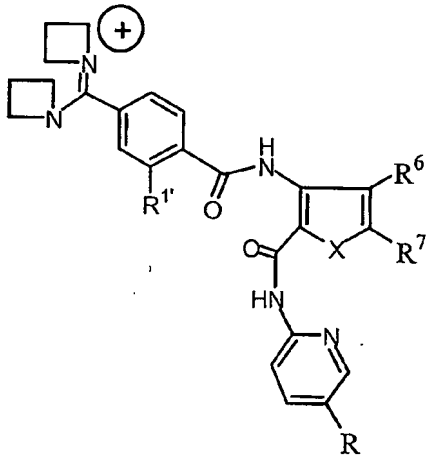
R is a -Cl, -Br, -I or –F,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formulae (I-VI) having the following structure:



or



wherein:

$R^{1'}$ is a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, SMe, SO_2Me, or SO_2NH_2;

R^2 is a H, -Cl, -Br, -I, -F or -O-C_{1-6}alkyl;

R^4 is a H, -Cl, -Br, -I, -F, -O-C_{1-6}alkyl, -NH-C_{1-6}acyl, -NO_2, -$NHSO_2$-C_{1-4}alkyl, -CN or -O-$(CH_2)_{1-4}$-COOH;

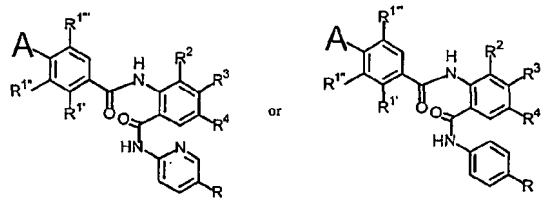
X is -O- or -S-;

R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -O-C_{1-6}alkyl; and

R is a -Cl, -Br, -I or -F;

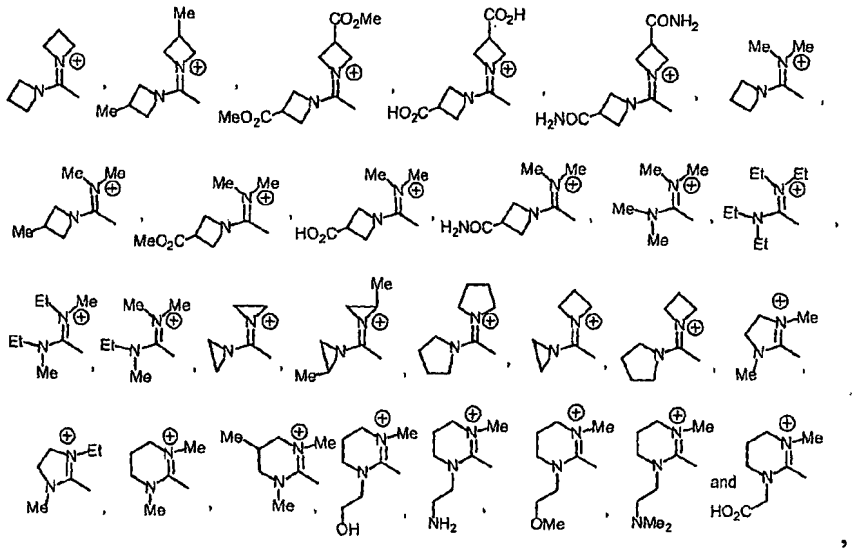
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides compounds of the formula (I-VI) having the following structure:



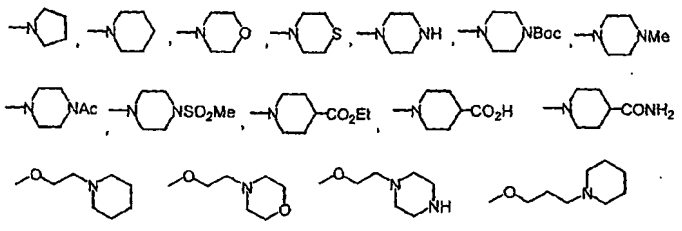
wherein:

A is a member selected from the group consisting of:



$R^{1'}$, $R^{1''}$, and $R^{1'''}$ are independently a H, -F, -Cl, -Br, -Me, -CF_3, -OH, -OMe, -OCF_3, -OEt, -OPr^n, -OPr^i, -OBu^t, -NO_2, -CN, -OCH_2CO_2H, -OCH_2CO_2Me, -NH_2, -NHMe, -NMe_2, -$NHSO_2Me$, -NHCOMe, -$NHCO(CH_2)_2NH_2$, -SMe, -SO_2Me, -SOMe, or -SO_2NH_2;

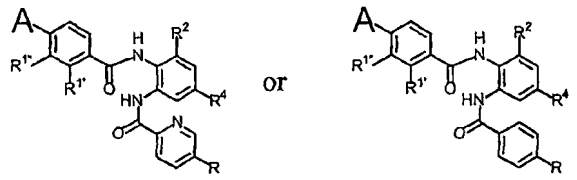
R^2, R^3, R^4, and R^5 are independently a H, -F, -Cl, -Br, -CH_3, -CF_3, -OH, -OMe, -OCF_3, -NH_2, -NHMe, -NMe_2, -OCH_2CH_2OH, -OCH_2CH_2OMe, -$OCH_2CH_2NH_2$, -OCH_2CH_2NHMe, -$OCH_2CH_2NMe_2$, -$OCH_2CH_2CH_2OMe$, -$OCH_2CH_2CH_2NMe_2$, -OCH_2COOH, -OCH_2COOEt, -OCH_2CH_2COOH, -OCH_2CH_2COOEt, -$NHCH_2COOH$, -$NHCH_2COOEt$, -$NMeCH_2COOH$, -$NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, -$NMeCH_2CH_2COOEt$, -NMeEt, -$NMeCH_2CH_2OH$, -$NMeCH_2CH_2OMe$, -NO_2, -NHAc, -$NHSO_2Me$, -SMe, -SO_2Me, -SOMe, -SO_2NH_2,



R is a H, -F, -Cl, -Br, -OMe, -OH, -NH_2, or –Me,

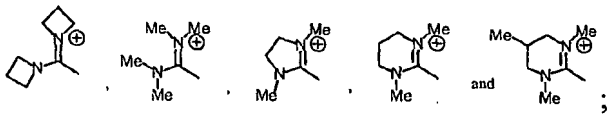
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formula (I-VI) having the following structure:



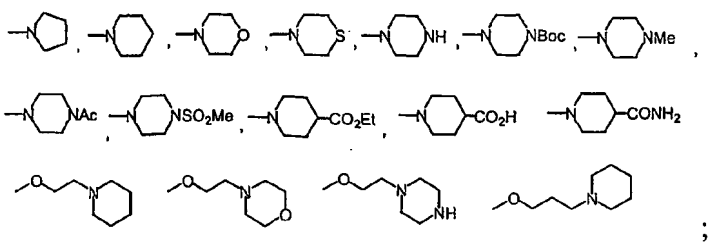
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ and $R^{1''}$ are independently a H, -F, -Cl, -Br, -Me, -CF_3, -OH, -OMe, -OCF_3, -OEt, -OPr^n, -OPr^i, -OBu^t, -NO_2, -CN, -OCH_2CO_2H, -OCH_2CO_2Me, -NH_2, -NHMe, -NMe_2, -$NHSO_2Me$, -NHCOMe, -$NHCO(CH_2)_2NH_2$, -SMe, -SO_2Me, -SOMe, or -SO_2NH_2;

R^2, and R^4 are independently a H, -F, -Cl, -Br, -CH_3, -CF_3, -OH, -OMe, -OCF_3, -NH_2, -NHMe, -NMe_2, -OCH_2CH_2OH, -OCH_2CH_2OMe, -$OCH_2CH_2NH_2$, -OCH_2CH_2NHMe, -$OCH_2CH_2NMe_2$, -$OCH_2CH_2CH_2OMe$, -$OCH_2CH_2CH_2NMe_2$, -OCH_2COOH, -OCH_2COOEt, -OCH_2CH_2COOH, -OCH_2CH_2COOEt, -$NHCH_2COOH$, -$NHCH_2COOEt$, -$NMeCH_2COOH$, -$NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, -$NMeCH_2CH_2COOEt$, -NMeEt, -$NMeCH_2CH_2OH$, -$NMeCH_2CH_2OMe$, -NO_2, -NHAc, -$NHSO_2Me$, -SMe, -SO_2Me, -SOMe, -SO_2NH_2,

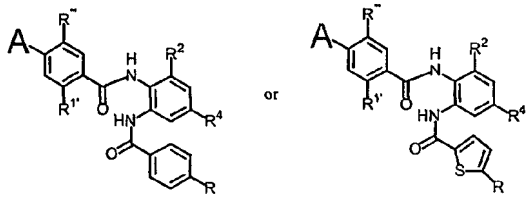


;

R is a H, -F, -Cl, or -Br,

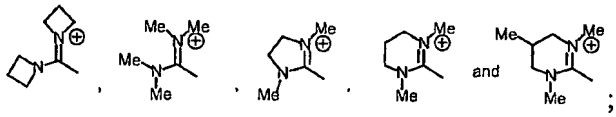
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formulae (I-VI) having the following structure:



wherein:

A is a member selected from the group consisting of:

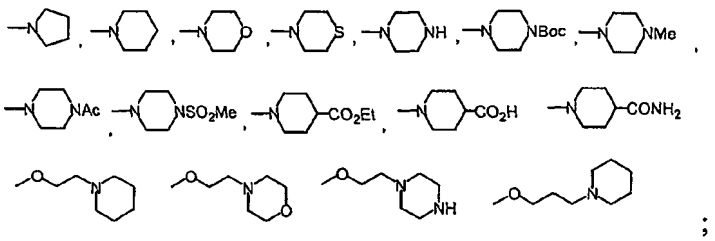


;

$R^{1'}$ and $R^{1'''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, -

OCH_2CH_2NHMe, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, $-NMeEt$, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, $-NHAc$, $-NHSO_2Me$, $-SMe$, $-SO_2Me$, $-SOMe$, $-SO_2NH_2$,

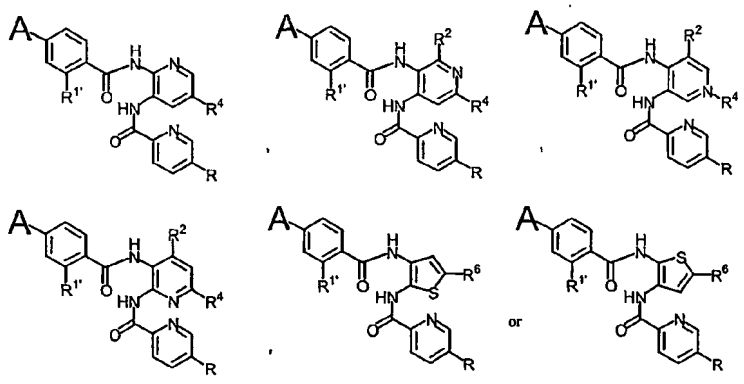


;

R is H, -F, -Cl, or –Br,

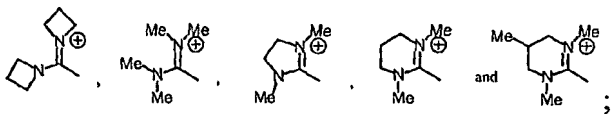
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides compounds of the formulae (I-VI) having the following structure:



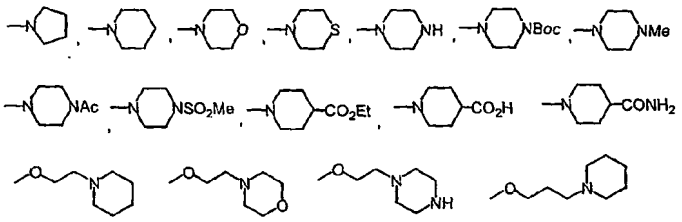
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

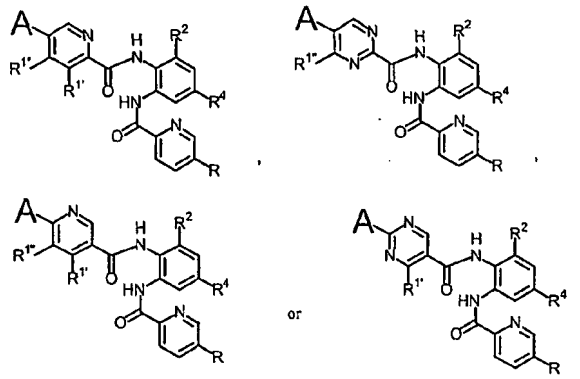
R^2, R^4, and R^6 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



R is a H, -F, -Cl, or –Br,

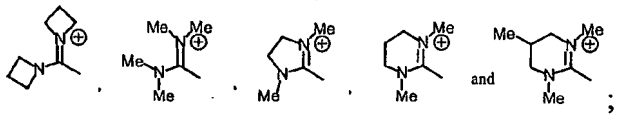
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides a compound of the formula (I-VI) having the following structure:



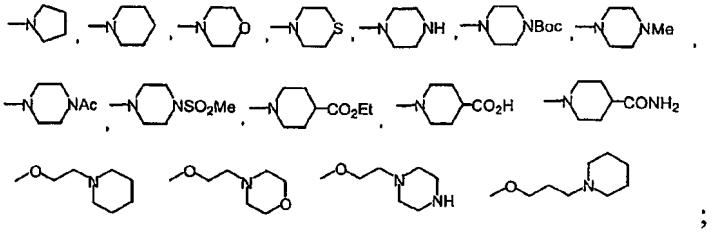
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ and $R^{1''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

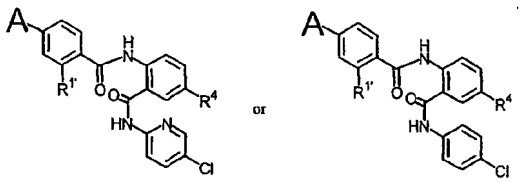
R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



R is a H, -F, -Cl, or –Br,

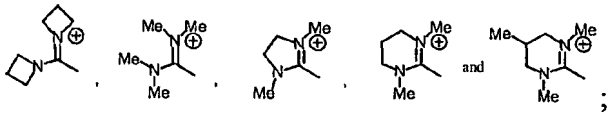
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides compounds of the formula (I-VI) having the following structure:



wherein:

A is a member selected from the group consisting of:

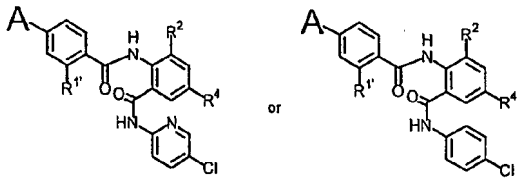


$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

R^4 is a H, -F, -Cl, -Br, -Me, -OH, -OMe, $-OCF_3$, $-OCH_2COOH$, $-OCH_2COOEt$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$,

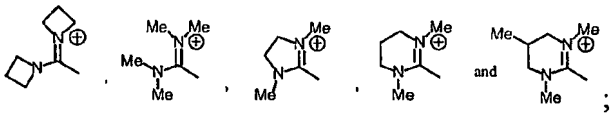
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides compounds of the formula (I-VI) having the following structure:



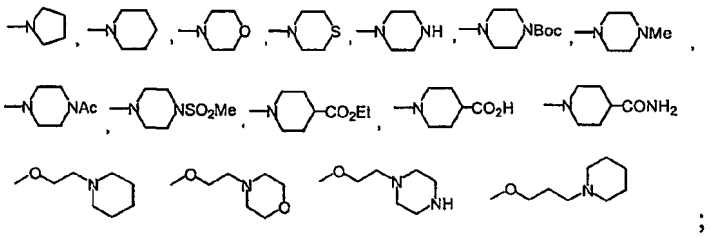
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

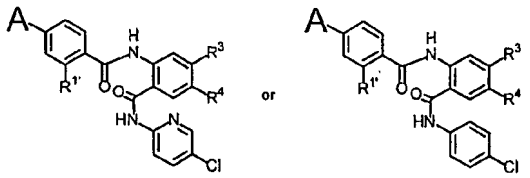
R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



R^4 is a -Br or –Cl,

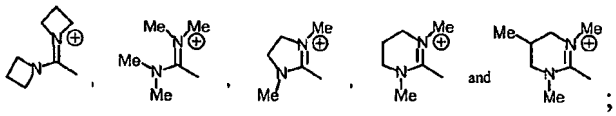
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention further provides compounds of the formula (I-VI) having the following structure:



wherein:

A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

R^3 and R^4 is a H, -F, -Cl, -Br, -Me, -OH, -OMe, $-OCF_3$, $-OCH_2COOH$, $-OCH_2COOEt$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$, all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives of the compounds of the invention as set forth herein. The compounds of the invention can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates and prodrug derivatives of such isomers and tautomers.

The compounds of the invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of the invention. Non-toxic and physiologically compatible salts

are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts of the compounds as described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulae above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

The invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of the invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of the invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base

derivative. Moreover, the prodrug derivatives of the invention may be combined with other features herein taught to enhance bioavailability.

The compounds of the present invention may also be used alone or in combination or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of the invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of the invention can be utilized *in vivo*, ordinarily in mammals such as primates (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of the invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of the invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of the invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition,

the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Preparation of Compounds

The compounds of the present invention may be synthesized by standard organic chemical synthetic methods as described and referenced in standard textbooks. These methods are well known in the art. See, e.g., Morrison and Boyd, "Organic Chemistry", Allyn and Bacon, Inc., Boston, 1959, et seq.

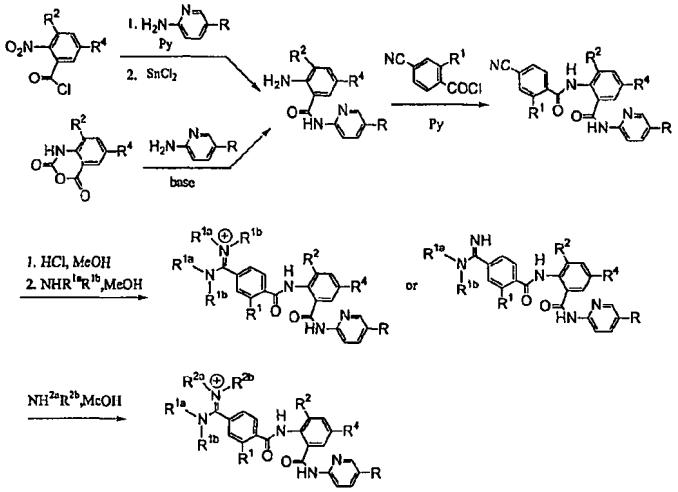
Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

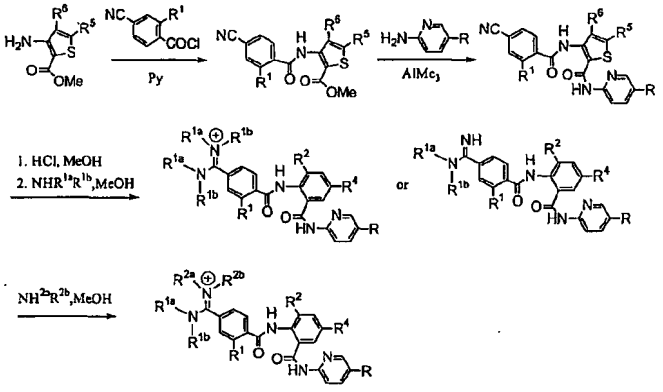
During the synthesis of these compounds, the functional groups of the substituents are optionally protected by blocking groups to prevent cross reaction during coupling procedures. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Non-limiting exemplary synthesis schemes are outlined directly below, and specific steps are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

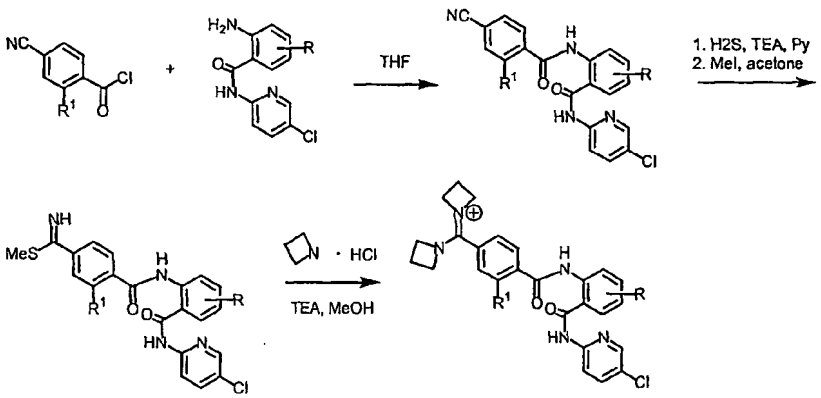
SCHEME 1



SCHEME 2

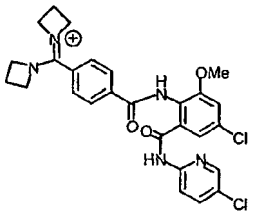


SCHEME 3



Example 1

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-methoxy-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.



Step 1: To a mixture of 3-methoxy-2-nitrobenzoic acid (75 g) and 2-amino-5-chloropyridine (53.8 g) in 1 L of pyridine at rt was added 43 mL of $POCl_3$ dropwise over 10 min. The mixture was stirred for 40 min and quenched by addition of 500 mL of ice-water. The precipitate was filtered and washed with portions of water until colorless and dried to give N-(5-chloro-2-pyridinyl)-2-nitro-3-methoxyphenylcarboxamide in 85% yield.

Step 2: A solution of N-(5-chloro-2-pyridinyl)-2-nitro-3-methoxyphenylcarboxamide (37 g) in 350 mL of THF and 350 mL of dioxane at 55-

65 °C was charged with 185 g of sodium hydrosulfite (85% tech. Grade) in 750 mL of water. The mixture was allowed to cool to rt after 2h and the organic layer was separated and treated with 185 g of sodium hydrosulfite in 750 mL of water again at 55-65 °C for 1h. The mixture was cooled to rt and the upper organic layer was separated and precipitated by addition of 700 mL of water. The precipitate was filtered and dried to give N-(5-chloro-2-pyridinyl)-2-amino-3-methoxyphenylcarboxamide in 75% yield.

Step 3. A solution of N-(5-chloro-2-pyridinyl)-2-amino-3-methoxyphenylcarboxamide (15.96 g) in 600 mL of toluene at 70-75 °C was charged with 8.23 g of NCS over 1h. The mixture was stirred for 2h and was allowed to cool to rt. The precipitate was filtered and washed with 200 mL of 0.5 M K_3PO_4 twice and 200 mL of water, and dried to give N-(5-chloro-2-pyridinyl)-2-amino-3-methoxy-5-chlorophenylcarboxamide in 95% yield.

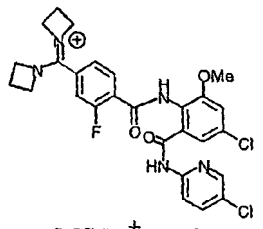
Step 4. A solution of N-(5-chloro-2-pyridinyl)-2-amino-3-methoxy-5-chlorophenyl carboxamide (57.6 g) in 250 mL of THF was charged with 4-cyano-2-fluorobenzoyl chloride (1 eq) in 100 mL of THF over 5 min. Hexane (400 mL) was added after 2h and the precipitate was filtered and washed with 40 mL of hexane three times and dried to give N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide (98%).

Step 5: A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide (50 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and azetidine.HCl (50 mg), triethylamine (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was

purified by RP_HPLC to give the target compound as a TFA salt. MS found $C_{27}H_{26}Cl_2N_5O_3$ M^+=538.

Example 2

(2-{[4-(azetidinylazetidinylidenemethyl)-2-fluorophenyl]carbonylamino}-3-methoxy-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

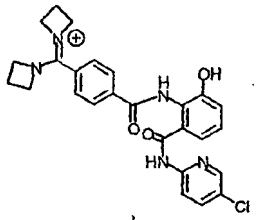


MS M^+: 556

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyano-2-fluorophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide.

Example 3

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide.



MS M^+: 490

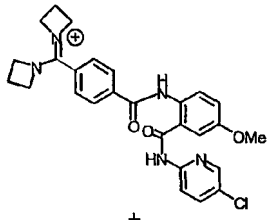
Step 1. A solution of N-(5-chloro-2-pyridinyl)-2-amino-3-methoxyphenyl carboxamide (177 mg, 1 mmol, 1 equiv) in 25 mL of THF was charged with 4-cyanobenzoyl chloride (165 mg, 1 equiv.) in 10 mL of THF over 5 min. Hexane (400 mL) was added after 2h and the precipitate was filtered and washed with 10 mL of hexane and dried to give N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-methoxyphenylcarboxamide.

Step 1. A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-methoxyphenylcarboxamide (120 mg, 3 mmol) in 25 mL of methylenechloride was treated with 15 mL of 1N of BBr_3 (5 equiv) in methylenechloride overnight at rt. The mixture was then poured into ice-water and the solid was filtered and dried to give N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-hydroxyphenylcarboxamide.

Step 5: A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-hydroxyphenylcarboxamide (39 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and azetidine.HCl (50 mg), triethylamine (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the target compound as a TFA salt. MS found $C_{26}H_{25}ClN_5O_3$ M^+=490.

Example 4

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide.



MS M^+: 505

Step 1: To a solution of 5-methoxy-2-nitrobenzoic acid (5.0 gm, 25 mmol) and 2-amino-5-chloropyridine (4.5 gm, 35 mmol) in anhydrous pyridine (50 mL) at 0°C was added $POCl_3$ (4.6 mL, 50 mmol). After stirring at room temperature for 30min, the reaction was complete. The mixture was quenched with water, concentrated and

diluted with EtOAc (200 mL). The organic solution was washed with brine, dried and evaporated to give compound **1** (5.5 gm, 66%). MS found for $C_{13}H_{10}ClN_3O_4$ $(M+H)^+$: 308.1.

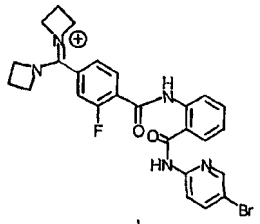
Step 2: A mixture of compound **1** (3.0 gm, 10 mmol) and $SnCl_2 \cdot 2H_2O$ (9.0 gm, 40 mmol) in EtOAc (100 mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (200 mL), and the red solution was washed with 1N aq. NaOH solution (x3) and brine, dried and evaporated to give compound **2** (1.8 gm, 67%). MS found for $C_{13}H_{12}ClN_3O_2$ $(M+H)^+$: 278.

Step 3: To a solution of compound **2** (1.5 gm, 5.4 mmol) in a mixture of pyridine (5 mL) and CH_2Cl_2 (30 mL) was added 4-cyanobenzoyl chloride (1.0 gm, 6.5 mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with CH_2Cl_2. After drying in vaccuo, compound **3** was obtained as a yellow solid in 82% yield (1.8 gm). MS found for $C_{21}H_{15}ClN_4O_3$ $(M+H)^+$: 407.0.

Step 4: To the suspension of compound **3** (200 mg) in a mixture of anhydrous MeOH (5 mL) and EtOAc (5 mL) at 0°C was bubbled anhydrous HCl gas to saturation. The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (5 mL) and separated into three portions. A mixture of azetidine (200 μL) and HOAc (300 μL) was added to one of the portions. The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give 15 mg of the title compound **4**. MS found for $C_{27}H_{27}ClN_5O_3$ M^+: 504.1.

Example 5

(2-{[4-(azetidinylazetidinylidenemethyl)-2-fluorophenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide.

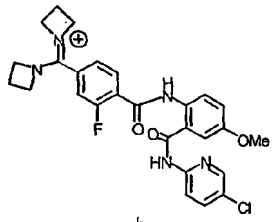


MS M^+: 537

This compound was prepared according to the procedure described above starting from N-(5-bromo-2-pyridinyl)-2-(4-cyano-2-fluorophenylcarbonyl)aminophenylcarboxamide.

Example 6

(2-{[4-(azetidinylazetidinylidenemethyl)-2-fluorophenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide.



MS M^+: 522

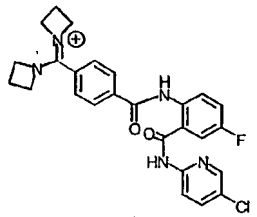
Step 1: A suspension of 4-cyano-2-fluorobenzoic acid (500 mg, 3.0 mmol) in thionyl chloride (4 mL) was refluxed until all solid went to solution, about 1 hr. The solvent was removed to get 4-cyano-2-fluoro-benzoyl chloride as a white solid. To a solution of compound 2 (600 mg, 2.16 mmol) in a mixture of pyridine (2 mL) and CH_2Cl_2 (20 mL) was added 4-cyano-2-fluorobenzoyl chloride (3.0 mmol). Reaction was completed after stirring overnight. The solvent was evaporated and the residue was triturated with EtOAc. The resulting solid was collected by filtration. After drying, N-(5-chloro(2-pyridyl)){2-[(4-cyano-2-fluorophenyl)carbonylamino]-5-methoxyphenyl}carboxamide was obtained as a yellow solid in 75% yield (980 gm). MS found for $C_{21}H_{14}ClFN_4O_3$ $(M+H)^+$: 425.0.

Step 2: To a solution of N-(5-chloro(2-pyridyl)){2-[(4-cyano-2-fluorophenyl)carbonylamino]-5-methoxyphenyl}carboxamide (100 mg) in 10%

Et_3N/pyridine (10 mL) at 0°C was bubbled dry H_2S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness. The residue was suspended in anhydrous acetone (10 mL), followed by addition of MeI (1 mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. The residue was dissolved in anhydrous MeOH (5 mL). A mixture of azetidine (200 μL) and AcOH (300 μL) in MeOH (2 mL) was added to the solution. The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound. MS found for $C_{27}H_{26}ClFN_5O_3$ M^+: 522.1.

Example 7

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-5-fluorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

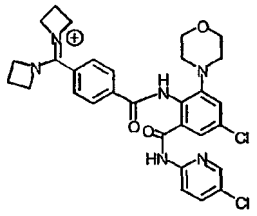


MS M^+: 492

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-5-fluorophenylcarboxamide.

Example 8

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(morpholin-1-yl)-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.



Step1. To a solution of 3,5-dichlorobenzoic acid (25 g, 1 equiv) in 125 mL of concentrated sulfuric acid at 0 °C was added concentrated HNO_3 (70% in H_2O, 11.9 g, 1.1 equiv) dropwise. The mixture was stirred at 0 °C to rt overnight, and then poured into ice-water. The suspension was then filtered and the solid was washed with cold water and dried to give 2-nitro-3,5-dichlorobenzoic acid (28 g, 94%). MS found for $C_7H_2Cl_2NO_4$ $(M-H)^-$: 226.

Step 2: A solution of 2-nitro-3,5-dichlorobenzoic acid (10.33 g, 44 mmol) and $(COCl)_2$ (22 g, 3 equiv) was dissolved in dichloromethane (100 mL), five drops of N,N-dimethylformamide was added and the mixture was stirred at r.t. for two hours. The volatile was evaporated and 11.6 g (44 mmol, 1 equiv) of the residue was redissolved in 80 mL of methylenechloride. To the solution was added 2-amino-5-chloropyridine (5.7g, 1eq) and pyridine (18mL, 5eq). After stirring overnight, the mixture was diluted with CH_2Cl_2, and washed with water, dried with Na_2SO_4, filtered and evaporated to give N-(5-chloro-2-pyridinyl)-2-nitro-3,5-dichlorophenylcarboxamide (15 g, 86%), which was used in the next step directly. MS found for $C_{12}H_7Cl_3N_3O_3$ $(M+H)^-$: 346.

Step 3. A mixture of N-(5-chloro-2-pyridinyl)-2-nitro-3,5-dichlorophenylcarboxamide (1.03 g, 3 mmol), morpholine (0.32 mL, 1.2 eq) and DIEA (1.05 mL, 2eq) was stirred in methyl sulfoxide (20mL) at 120 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with water and extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium carbonate. Column separation over silica gel gave N-(5-chloro-2-pyridinyl)-2-nitro-3-morpholino-5-chlorophenylcarboxamide (420 mg, 36%). MS found for $C_{16}H_{15}Cl_2N_4O_4$ $(M+H)^-$: 397.

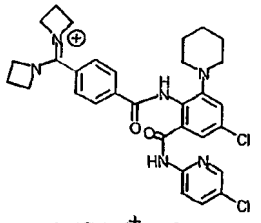
Step 4. A N-(5-chloro-2-pyridinyl)-2-nitro-3-morpholino-5-chlorophenylcarboxamide (396 mg, 1 mmol) and tin(II) chloride·$2H_2O$ (675 mg, 3eq) was refluxed in ethyl acetate (20 mL) for one hour. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, and dried over sodium

carbonate. The residue after concentration was taken up in 15 mL of THF, and to the solution was added 4-cyanobenzoyl chloride (180 mg, 1 equiv). The mixture was stirred at rt overnight and evaporated to give N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-morpholino-5-chlorophenylcarboxamide (490 mg, 98%). MS found for $C_{24}H_{20}Cl_2N_5O_3$ $(M+H)^+$: 496.

Step 5: A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-morpholino-5-chlorophenylcarboxamide (49 mg, 0.1 mmol) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and azetidine.HCl (50 mg), triethylamine (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the title compound (33 mg, 61%). MS found $C_{30}H_{31}Cl_2N_6O_3$ M^+=593.

Example 9

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(piperidin-1-yl)-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

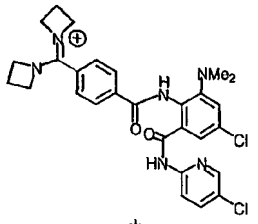


MS M^+: 592

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-(piperidin-1-yl)-5-chlorophenylcarboxamide.

Example 10

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-dimethylamino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

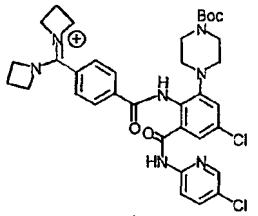


MS M^+: 552

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-dimethylamino-5-chlorophenylcarboxamide.

Example 11

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(4-N-Boc-piperazin-1-yl)-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

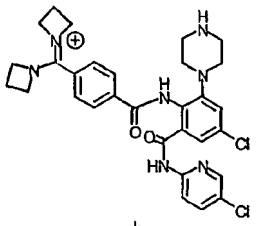


MS M^+: 693

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-(4-N-Boc-piperazin-1-yl)-5-chlorophenylcarboxamide.

Example 12

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(piperazin-1-yl)-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

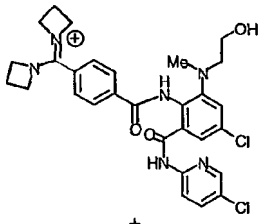


MS M^+: 593

This compound was prepared by treating the compound in Example 11 with 4N HCl in dioxane at rt overnight followed by RP-HPLC purification.

Example 13

(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(N-methyl-N-(2-hydroxyethyl)amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

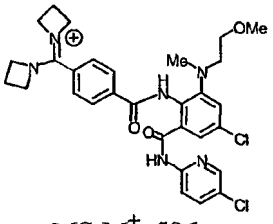


MS M^+: 582

This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-(N-methyl-N-2-hydroxyethyl)amino-5-chlorophenylcarboxamide.

Example 14

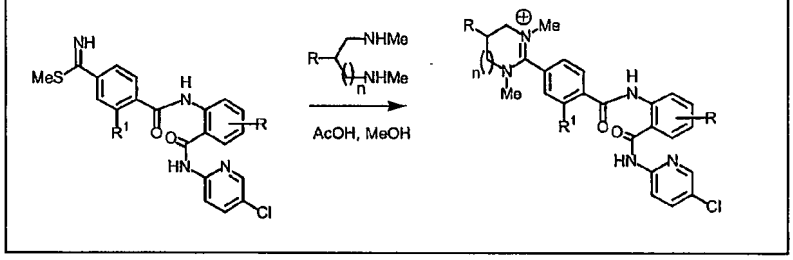
(2-{[4-(azetidinylazetidinylidenemethyl)phenyl]carbonylamino}-3-(N-methyl-N-(2-methoxyethyl)amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.



MS M^+: 596

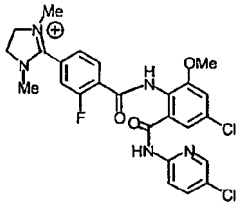
This compound was prepared according to the procedure described above starting from N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-3-(N-methyl-N-2-methoxyethyl)amino-5-chlorophenylcarboxamide.

SCHEME 4



Example 15

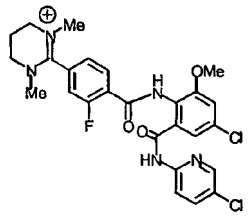
N-{4-chloro-6-methoxy-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[1,3-dimethyl(2-imidazolin-2-yl)]phenyl}carboxamide



A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyano-2-fluorophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide (45 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and a premixed solution of N,N'-dimethylethylenediamine (0.5 mL) and AcOH (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the target compound as a TFA salt (35 mg, 66%). MS found $C_{25}H_{23}Cl_2FN_5O_3$ M^+=530.

Example 16

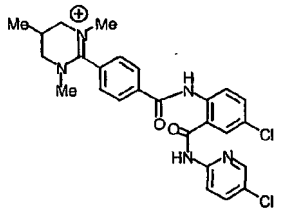
N-{4-chloro-6-methoxy-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-(1,3-dimethyl-3,4,5,6-tetrahydropyrimindin-2-yl))-2-fluorophenylphenyl}carboxamide.



A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyano-2-fluorophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide (45 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and a premixed solution of N,N'-dimethylpropylenediamine (0.5 mL) and AcOH (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the target compound as a TFA salt (38 mg, 70%). MS found $C_{26}H_{25}Cl_2FN_5O_3$ M^+=544.

Example 17

N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-(1,3-dimethyl-5-methyl-3,4,5,6-tetrahydropyrimindin-2-yl))phenylphenyl}carboxamide.



Step 1: To a solution of 2-amino-5-chloropyridine (328mg, 2.55mmol) in tetrahydrofuran (5ml) was 0.5 M potassium bis(trimethylsilyl)amide in toluene (10ml, 5.05mmol) dropwise at –78 °C. After stirred for additional 0.5hr at –78 °C, the mixture was added 5-chloroisatoic anhydride (0.5g, 2.55mmol) at –78 °C. The

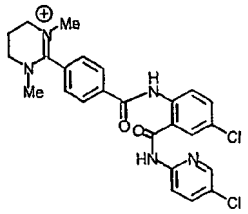
mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g. 100%). MS found for C12H9Cl2N3O M^+=282, $(M+2)^+$=284.

Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 2.52mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (417mg, 2.52mmol) and pyridine (0.611ml, 7.55mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as a solid (683mg, 66%). MS found for C20H12Cl2N4O2 M^+=411, $(M+2)^+$=413.

Step 3: A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-5-chlorophenylcarboxamide (41 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and a premixed solution of N,N'-dimethyl-2-methylpropylenediamine (0.5 mL) and AcOH (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the target compound as a TFA salt (41 mg, 80%). MS found $C_{26}H_{25}Cl_2N_5O_2$ M^+=509.

Example 18

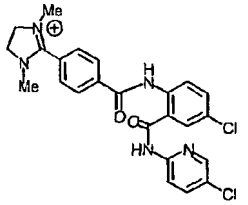
N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-(1,3-dimethyl-3,4,5,6-tetrahydropyrimindin-2-yl))phenylphenyl}carboxamide.



A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-5-chlorophenylcarboxamide (41 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and a premixed solution of N,N'-dimethylpropylenediamine (0.5 mL) and AcOH (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude residue was purified by RP_HPLC to give the target compound as a TFA salt (38 mg, 77%). MS found $C_{25}H_{23}Cl_2N_5O_2$ M^+=495.

Example 19

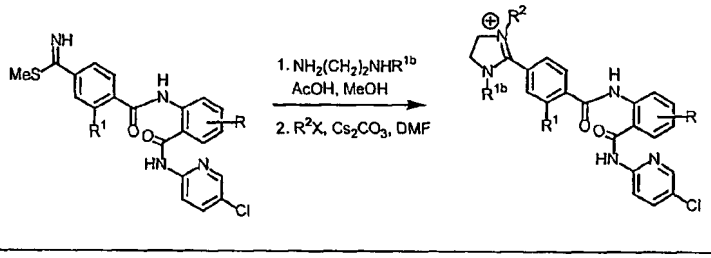
N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[1-methyl-3-methyl(2-imidazolin-2-yl)]phenyl}carboxamide



A solution of N-(5-chloro-2-pyridinyl)-2-(4-cyanophenylcarbonyl)amino-5-chlorophenylcarboxamide (41 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0°C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration the residue was dissolved in anhydrous methanol (5 mL) and a premixed solution of N,N'-dimethylethylenediamine (0.5 mL) and AcOH (0.5 mL) were added. The mixture was refluxed for 15 min. After concentration, the crude

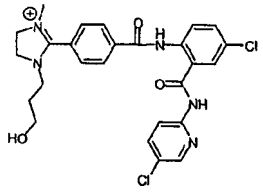
residue was purified by RP_HPLC to give the target compound as a TFA salt (33 mg, 69%). MS found $C_{24}H_{21}Cl_2N_5O_2$ M^+=481.

SCHEME 5



Example 20

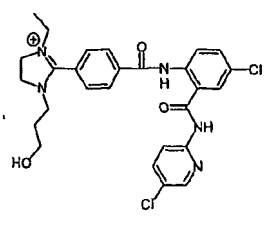
N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[1-(3-hydroxypropyl)-3-methyl(2-imidazolin-2-yl)]phenyl}carboxamide



To a solution of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[1-(3-hydroxypropyl)-2-imidazolin-2-yl]phenyl}carboxamide (20 mg, 0.036 mmol) in 1 mL DMF were added Cs_2CO_3 (10 mg) and MeI (7.5 mg, 0.053 mmol). The mixture was stirred for 2 hrs at room temperature and subjected to RP-HPLC purification to afford the title compound as a TFA salt. MS found for $C_{26}H_{26}Cl_2N_5O_3^+$ M^+ 526.

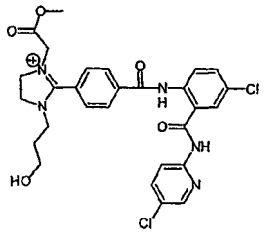
Examples 21-26

The following Examples 21-26 were similarly prepared by following the procedure of Example 20.



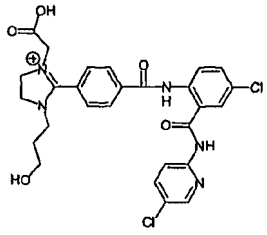
$C_{27}H_{28}Cl_2N_5O_3^+$

M^+=540



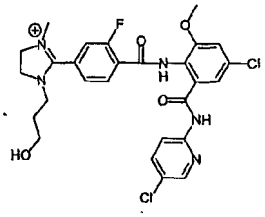
$C_{28}H_{28}Cl_2N_5O_5^+$

M^+=584



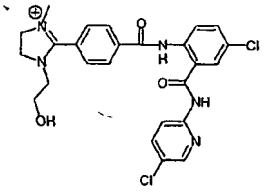
$C_{27}H_{26}Cl_2N_5O_5^+$

M^+=570



$C_{27}H_{27}Cl_2FN_5O_4^+$

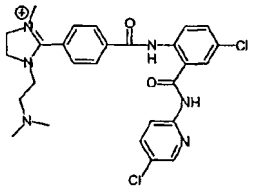
M^+=574



$C_{25}H_{24}Cl_2N_5O_3^+$

M^+=512

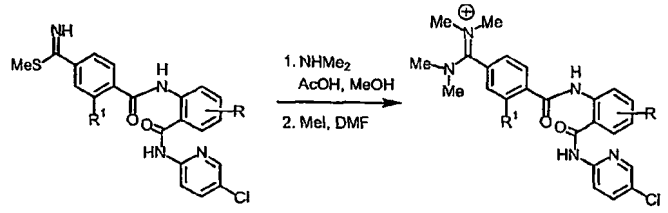
and



$C_{27}H_{29}Cl_2N_6O_2^+$

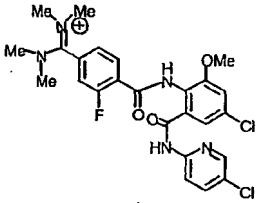
M^+=539

SCHEME 6



Example 27

(2-{[4-(dimethylaminodimethylaminoidenemethyl)-2-fluorophenyl]carbonylamino}-3-(N-methyl-N-(2-hydroxyethyl)amino-3-methoxy-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.



MS M^+: 532

A solution of N-(5-chloro-2-pyridinyl)-2-(4-N,N-dimethylamidino-2-fluorophenylcarbonyl)amino-3-methoxy-5-chlorophenylcarboxamide (30 mg) and MeI (2 mL) in 1 mL of DMF was at 120C (bath temperature) for 24 h. After removing all volatile, the residue was subjected to RP-HPLC to give the target compound (6 mg, 19%). MS found $C_{25}H_{25}Cl_2FN_5O_3$ M^+=532.

Compositions and Formulations

Compositions or formulations of the compounds of the invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween®, Pluronics® or polyethyleneglycol.

Dosage formulations of the compounds of the invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of the invention typically will be between about 3 and about 11, more preferably from about 5 to about 9 and most

preferably from about 7 to about 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of the invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of the invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage of the compounds and compositions of the invention range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of the invention may be administered several times daily. Other dosage regimens may also be useful (e.g. single daily dose and/or continuous infusion).

Typically, about 0.5 to about 500 mg of a compound or mixture of compounds of the invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor, etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as

microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation

which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of the invention are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. The compounds of this present invention, selected and used as disclosed herein, find utility as a diagnostic or therapeutic agent for preventing or treating a condition in a mammal characterized by undesired thrombosis or a disorder of coagulation. Disease states treatable or preventable by the administration of compounds of the invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, the treatment of reocclusion or restenosis of reperfused coronary arteries, thromboembolic complications of surgery and peripheral arterial occlusion, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

Accordingly, the invention provides a method for preventing or treating a condition in a mammal characterized by undesired thrombosis which administers to a mammal a therapeutically effective amount of a compound of the invention, as described herein. Conditions for prevention or treatment include, for example, (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated

intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of the invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Thus, the compounds of the invention also find utility in a method for inhibiting the coagulation of biological samples by administration of a compound of the invention.

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of the invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from about 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate

turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than about 500 nM in the factor Xa assay, preferably less than about 200 nM, and more preferred compounds have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than about 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than about 1.0 μM in the thrombin assay, preferably greater than about 10.0 μM, and more preferred compounds have an IC_{50} of greater than about 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate

of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. et al., Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

Effects of Compounds in Rabbit Venous Thrombosis model

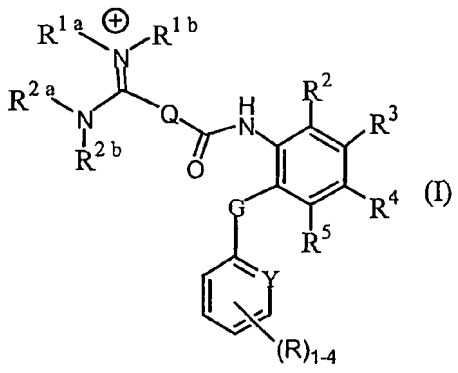
Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 μg/kg + 2.57 μg/kg/min). Compounds have no significant effects on hematological parameters as compared to saline controls. All measurements are

an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean ± SD.

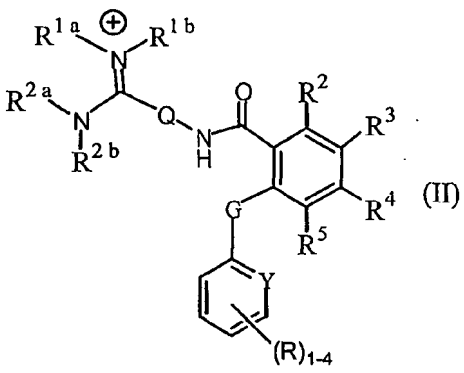
Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED IS:

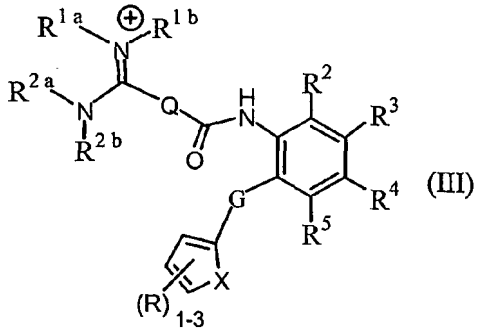
1. A compound of the general formulae (I), (II), (III), (IV), (V), or (VI):



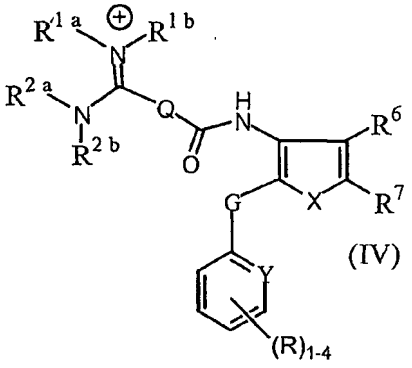
(I)



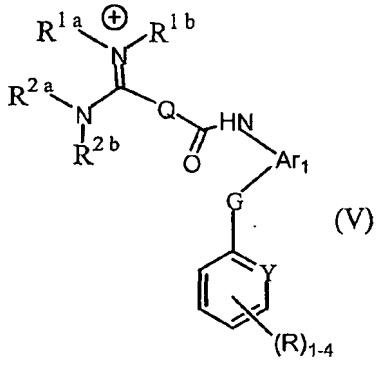
(II)



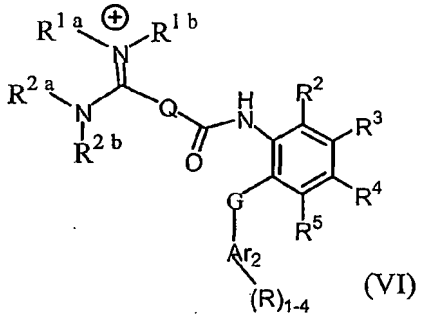
(III)



(IV)



(V)



(VI)

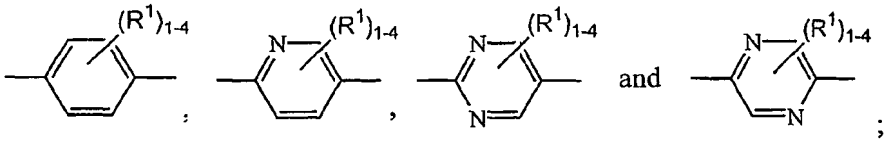
wherein:

R^{1a} and R^{1b} are each independently a member selected from the group consisting of:

C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{1a} and R^{1b} or R^{1a} and R^{2a}, as set forth below, taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or heteroaromatic quaternary amidino group, which optionally contains heteroatoms of N, O or S; R^{1a} or R^{1b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

R^{2a} and R^{2b} are each independently a member selected from the group consisting of: C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-8} cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-6}alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R^{2a} and R^{2b} or R^{2a} and R^{1a}, as set forth above, taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 3 to 8 membered heterocyclic or heteroaromatic amino group, which optionally contains heteroatoms of N, O or S; R^{2a} or R^{2b} is optionally substituted with at least one halo, alkyl, hydroxy, alkoxy, amide, ester, acid, alkylalkoxy, amino, nitro and cyano;

Q is a member selected from the group consisting of:



R^1 is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, haloC_{1-6}alkyl, -OH, -OC_{1-6}alkyl, -OhaloC_{1-6}alkyl, -NO_2, -CN, -OC_{1-6}alkylCOOH, -OC_{1-6}alkylCOOC_{1-6}alkyl, -OC_{1-6}alkylCONR_aR_b, -NR_aC_{1-6}alkylCOOH, -NR_aC_{1-6}alkylCOOC_{1-6}alkyl, -NR_aC_{1-6}alkylCONR_aR_b, -NR_aR_b, -NHSO_2C_{1-6}alkyl, -NHCOC_{1-6}alkyl, -NHCOC_{1-6}alkylNR_aR_b, –SC_{1-6}alkyl, -SO_2C_{1-6}alkyl, SOC_{1-6}alkyl, or –SO_2NR_aR_b;

R_a and R_b are independently H, -C_{1-6}alkyl, haloC_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl C_{3-8}cycloalkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylalkoxy, C_{1-6}alkylamine, C_{1-}

$_6$alkylcarboxyl, C_{1-6}alkylester, and C_{1-6}alkylamide; or R_a and R_b taken together with the nitrogen to which they are attached forms a heterocyclic or heteroaromatic amine group and which optionally contains heteroatoms of N, O or S and which is optionally substituted with –BOC, alkyl, acyl, -SO_2C_{1-6}alkyl, -CO_2C_{1-6}alkyl, -COOH, or –$CONR_aR_b$;

R^2, R^3, R^4, and R^5 are independently H, -Cl, -Br, -I, -F, C_{1-6}alkyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, -OH, -Ohaloalkyl, -NO_2, -NHAc, -$NHSO_2Me$, C_{1-6}alkylguanidino, C_{1-6}alkylamidino, -NR_aR_b, -OC_{1-6}alkylOH, -OC_{1-6}alkylOC_{1-6}alkyl, -OC_{1-6}alkylNR_aR_b, -NR_aC_{1-6}alkylOH, -NR_aC_{1-6}alkylOC_{1-6}alkyl, -NR_aC_{1-6}alkylNR_aR_b, -OC_{1-6}alkylCOOH, -OC_{1-6}alkyl$COOC_{1-6}$alkyl, -OC_{1-6}alkyl$CONR_aR_b$, -NR_aC_{1-6}alkylCOOH, -NR_aC_{1-6}alkyl$COOC_{1-6}$alkyl, -NR_aC_{1-6}alkyl$CONR_aR_b$, aryl, heteroary, -SC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, or -$SO_2NR_aR_b$, where R_a and R_b are each as set forth above;

Ar_1 is a six-membered aromatic heterocyclic ring containing 1-3 N atoms; the ring atoms are independently substituted by R^2, R^3, or R^4;

X is -O- or -S-;

G is –C(=O)NH- or –NHC(=O)-;

Y is CH or N;

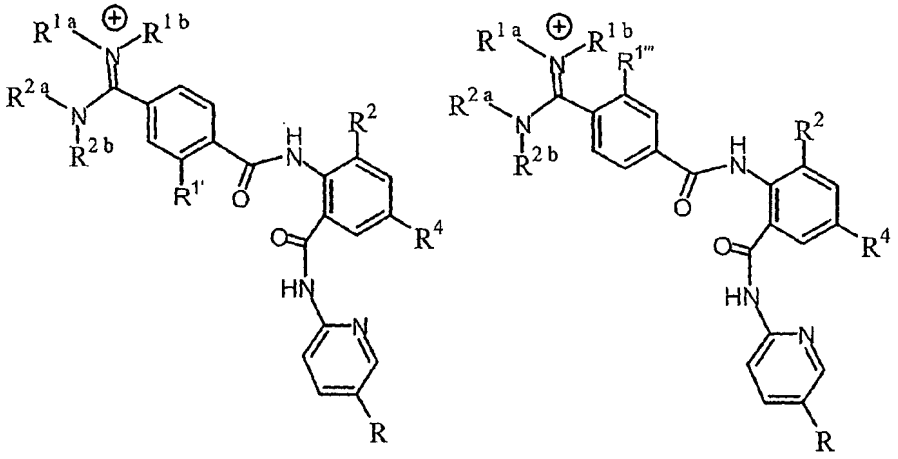
R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -OC_{1-6}alkyl; and

Ar_2 is a five or six-membered aromatic ring containing 1-3 hetero atoms selected from N, O, and S; The ring atoms are independently substituted by 1-4 R group;

R is a H, -Cl, -Br, -I, -F, -C_{1-6}alkyl, -OC_{1-6}alkyl, -OH, or -NR_aR_b, where R_a and R_b are each as set forth above;

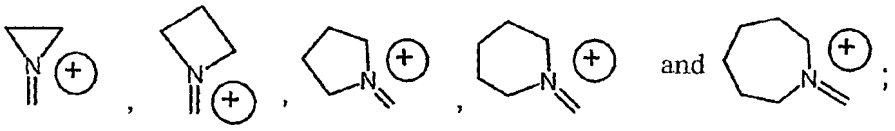
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1 having the following structure:

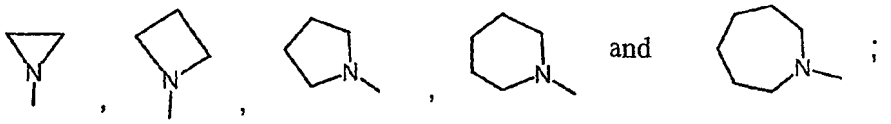


wherein:

R^{1a} and R^{1b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a quaternary ammonium group selected from the group consisting of:



R^{2a} and R^{2b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{2a} and R^{2b} taken together with the nitrogen atom to which they are attached form a heterocyclic amine group selected from the group consisting of:



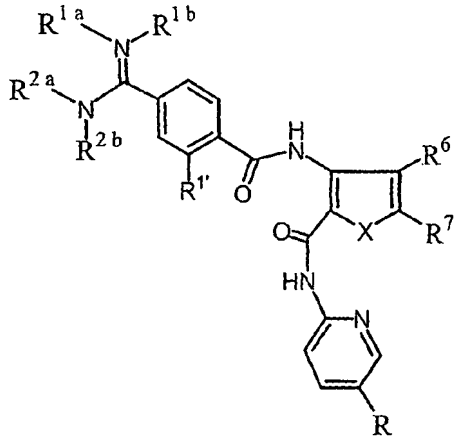
$R^{1'}$ and $R^{1'''}$ are independently a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, -CN, -COOH, -COOEt, CONH2, SMe, SO_2Me, or SO_2NH_2;

R^2 is a H, -Cl, -Br, -I, -F, $-NH_2$, NHMe, NMe_2, or -O-C_{1-6}alkyl; and

R^4 is a H, -Cl, -Br, -I, -F, -O-C_{1-6}alkyl, -NH-C_{1-6}acyl, $-NO_2$, $-NHSO_2$-C_{1-4}alkyl, -CN or -O-$(CH_2)_{1-4}$-COOH; and

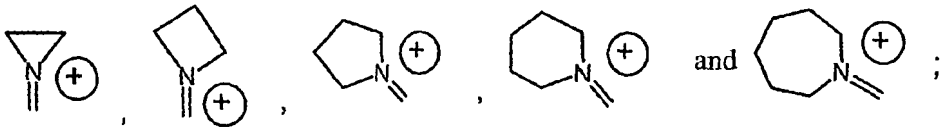
R is a -Cl, -Br, -I or –F.

3. A compound of claim 1 having the following structure:

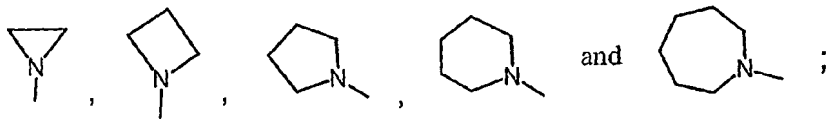


wherein:

R^{1a} and R^{1b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a quaternary ammonium group selected from the group consisting of:



R^{2a} and R^{2b} are each independently a $-CH_3$ or $-CH_2-CH_3$; or R^{2a} and R^{2b} taken together with the nitrogen atom to which they are attached form a heterocyclic amine group selected from the group consisting of:



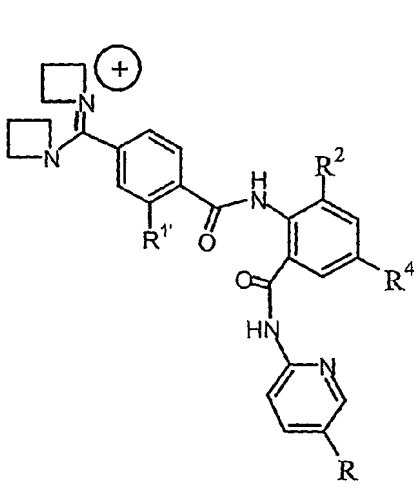
$R^{1'}$ is a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, SMe, SO_2Me, or SO_2NH_2;

X is -O- or -S-;

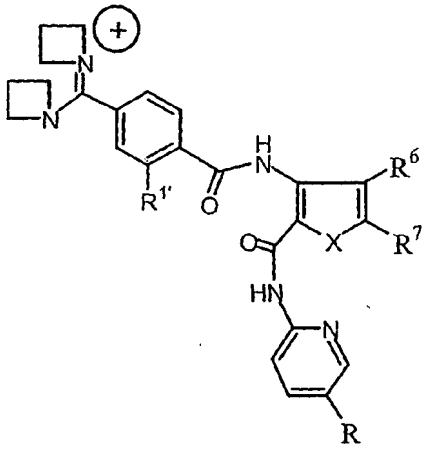
R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -OC_{1-6}alkyl; and

R is a -Cl, -Br, -I or –F.

4. A compound of claim 1 having the following structure:



or



wherein:

$R^{1'}$ is a H, -Cl, -Br, -I, -F, OMe, OCF_3, CH_3, CF_3, NH_2, NHMe, NMe_2, SMe, SO_2Me, or SO_2NH_2;

R^2 is a H, -Cl, -Br, -I, -F or -O-C_{1-6}alkyl;

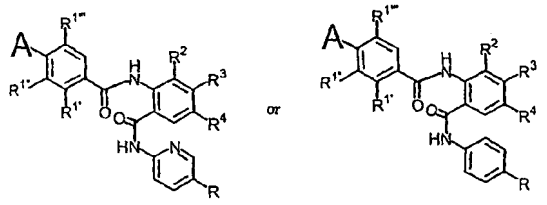
R^4 is a H, -Cl, -Br, -I, -F, -O-C_{1-6}alkyl, -NH-C_{1-6}acyl, -NO_2, -$NHSO_2$-C_{1-4}alkyl, -CN or -O-$(CH_2)_{1-4}$-COOH;

X is -O- or -S-;

R^6 and R^7 are each independently a H, -Cl, -Br, -I, -F or -O-C_{1-6}alkyl; and

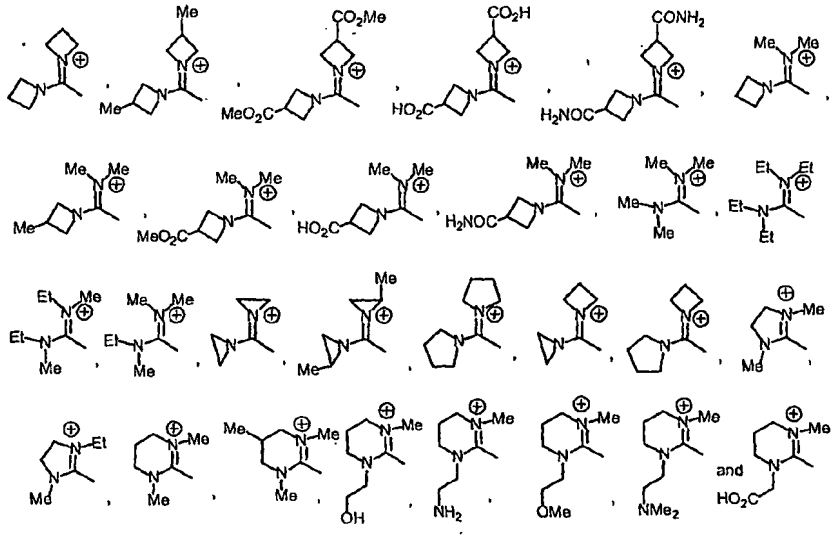
R is a -Cl, -Br, -I or –F.

5. A compound of claim 1 having the following structure:



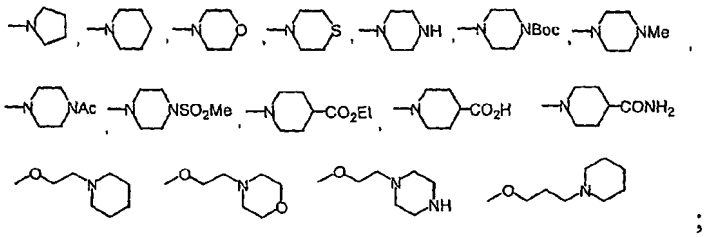
wherein:

A is a member selected from the group consisting of:



$R^{1'}$, $R^{1''}$, and $R^{1'''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, -COOH, -COOEt, -CONHMe, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

R^2, R^3, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,

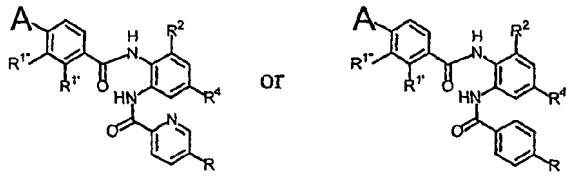


;

and

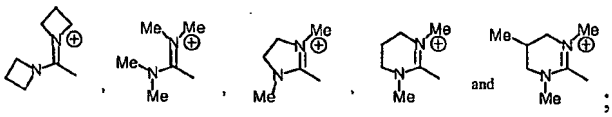
R is a H, -F, -Cl, -Br, -OMe, -OH, $-NH_2$, or –Me.

6. A compound of claim 1 having the following structure:



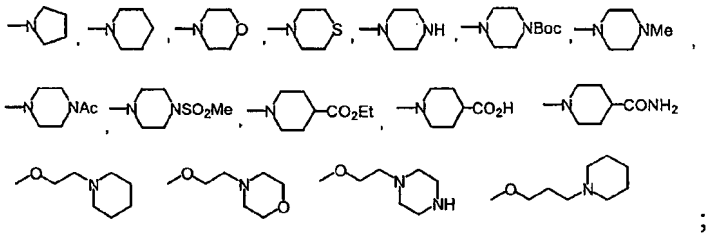
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ and $R^{1''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

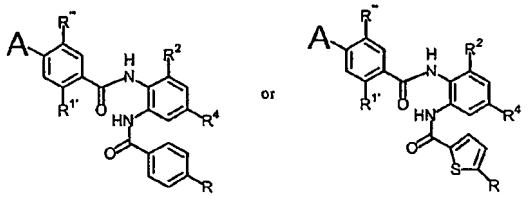
R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



and

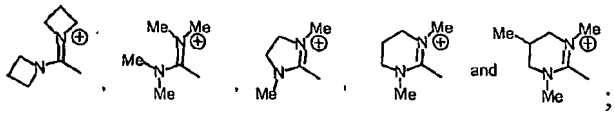
R is a H, -F, -Cl, or –Br.

7. A compound of claim 1 having the following structure:



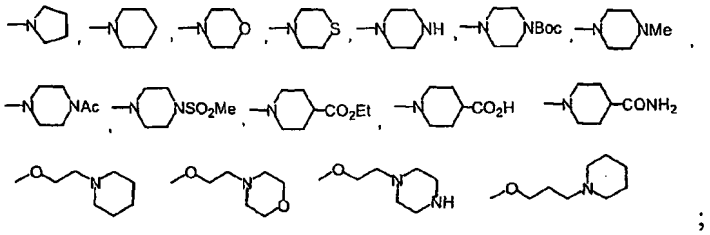
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ and $R^{1''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

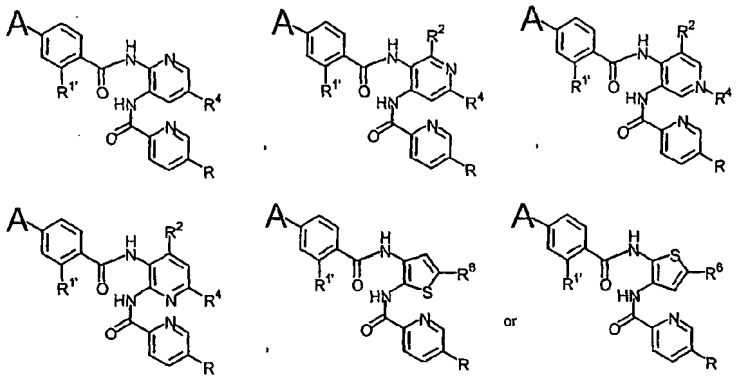
R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



and

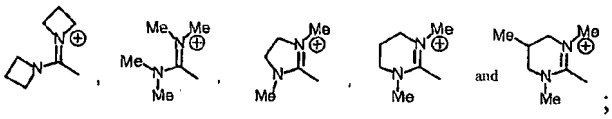
R is H, -F, -Cl, or –Br.

8. A compound of claim 1 having the following structure:



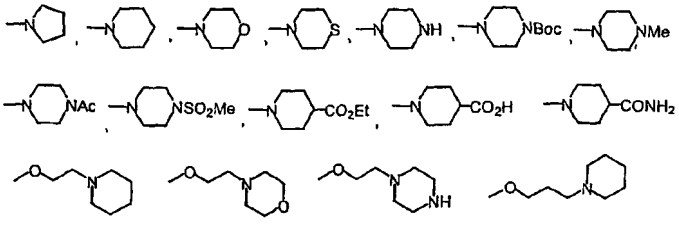
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

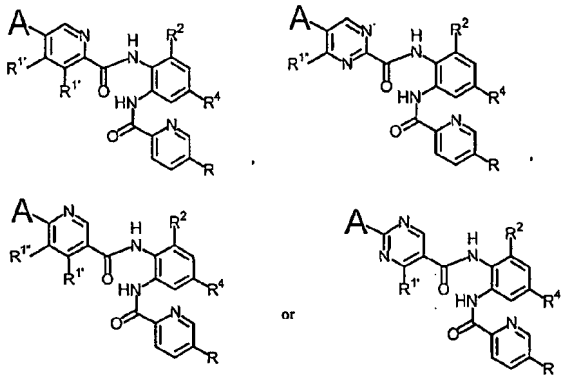
R^2, R^4, and R^6 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



and

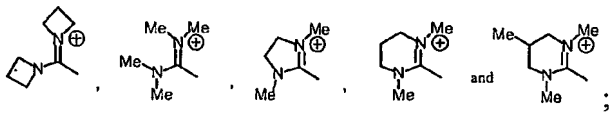
R is a H, -F, -Cl, or –Br.

9. A compound of claim 1 having the following structure:



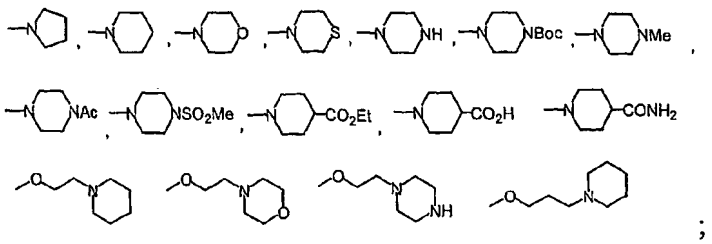
wherein:

A is a member selected from the group consisting of:



$R^{1'}$ and $R^{1''}$ are independently a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

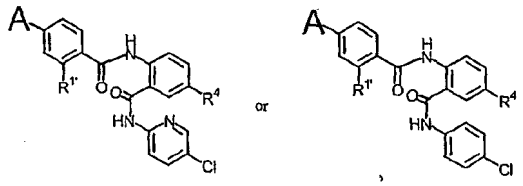
R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,



and

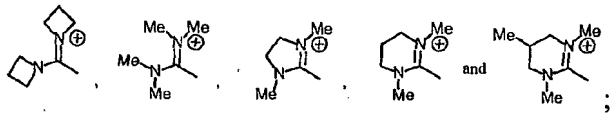
R is a H, -F, -Cl, or –Br.

10. A compound of claim 1 having the following structure:



wherein:

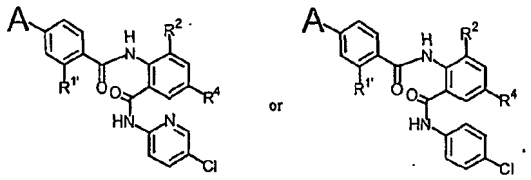
A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$; and

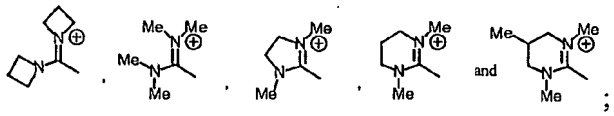
R^4 is a H, -F, -Cl, -Br, -Me, -OH, -OMe, $-OCF_3$, $-OCH_2COOH$, $-OCH_2COOEt$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$.

11. A compound of claim 1 having the following structure:



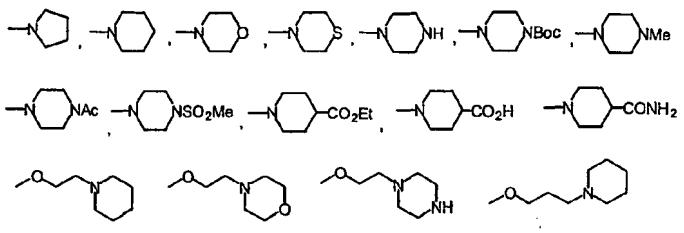
wherein:

A is a member selected from the group consisting of:

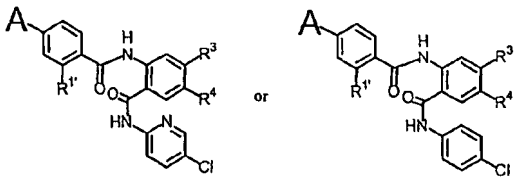


$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$;

R^2, and R^4 are independently a H, -F, -Cl, -Br, $-CH_3$, $-CF_3$, -OH, -OMe, $-OCF_3$, $-NH_2$, -NHMe, $-NMe_2$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2CH_2OMe$, $-OCH_2CH_2CH_2NMe_2$, $-OCH_2COOH$, $-OCH_2COOEt$, $-OCH_2CH_2COOH$, $-OCH_2CH_2COOEt$, $-NHCH_2COOH$, $-NHCH_2COOEt$, $-NMeCH_2COOH$, $-NMeCH_2COOEt$, $NMeCH_2CH_2COOH$, $-NMeCH_2CH_2COOEt$, -NMeEt, $-NMeCH_2CH_2OH$, $-NMeCH_2CH_2OMe$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, $-SO_2NH_2$,

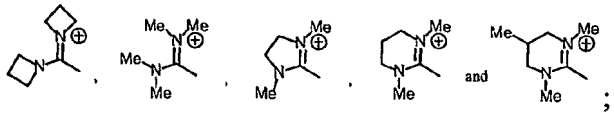


12. A compound of claim 1 having the following structure:



wherein:

A is a member selected from the group consisting of:



$R^{1'}$ is a H, -F, -Cl, -Br, -Me, $-CF_3$, -OH, -OMe, $-OCF_3$, -OEt, $-OPr^n$, $-OPr^i$, $-OBu^t$, $-NO_2$, -CN, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-NH_2$, -NHMe, $-NMe_2$, $-NHSO_2Me$, -NHCOMe, $-NHCO(CH_2)_2NH_2$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$; and

R^3 and R^4 is a H, -F, -Cl, -Br, -Me, -OH, -OMe, $-OCF_3$, $-OCH_2COOH$, $-OCH_2COOEt$, $-NO_2$, -NHAc, $-NHSO_2Me$, -SMe, $-SO_2Me$, -SOMe, or $-SO_2NH_2$.

13. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of one of claims 1-12.

14. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of one of claims 1-12.

15. The method of claim 14, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic

stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

16. A method for inhibiting the coagulation of biological samples comprising the administration of a compound of one of claims 1-12.